INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 06/35196

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) C07K 14/81 (2007.01)
USPC 435/219
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC 435/219

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC(8) C07K 14/81 (2007.01) IPC(8)C07K 14/81, C12Q 1/37, C12N 9/64
USPC 435/219, 435/183, 435/212, 435/195, 435/378, 435/381

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

DB=PGPB,USPT,USOC,EPAB,JPAB: (Proteasome and inhibit$ and lactam) and synthesis and (20S proteasome)
Google Scholar: Proteasome lactam synthesis inhibitor; Proteasome lactam synthesis; proteasome lactam synthesis author:corey OR author: hogan OR author: linek

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 6,214,862 B1 (Fenteany et. al.) 10 April 2001 (10.04.2001) (col. 2 line 43 to col. 3, line 23; col 8, lines 38-49; col. 59, lines 1-24; col 58, lines 15-18).	1, 4-6, 11-13, 17-20, 22 --- 14-16
Y	GOLDBERG, et al, "Not just research tools-proteasome inhibitors offer therapeutic promise", Nature Medicine, April 2002, Vol. 8, No. 4, Page 340 (col. 1, para. 2).	14-16

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 March 2007 (28.03.2007)	03 AUG 2007
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (April 2005)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: Ernest V. Linek
Banner & Witcoff, Ltd.
28 State Street - 28th Floor
Boston, Massachusetts 02109

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	03 AUG 2007
Applicant's or agent's file reference 004979.00053	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 06/35196	08 September 2006 (08.09.2006)	12 September 2005 (12.09.2005)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - C07K 14/81 (2007.01)
USPC - 435/219

Applicant President and Fellows of Harvard College

1. This opinion contains indications relating to the following items:

- [X] Box No. I Basis of the opinion
- [ ] Box No. II Priority
- [ ] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV Lack of unity of invention
- [X] Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI Certain documents cited
- [ ] Box No. VII Certain defects in the international application
- [ ] Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	28 March 2007 (28.03.2007)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into _____ , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing

      ☐ contained in the international application as filed

      ☐ filed together with the international application in electronic form

      ☐ furnished subsequently to this Authority for the purposes of search

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	2-3, 7-10, 14-16, 21, 23	YES
	Claims	1, 4-6, 11-13, 17-20, 22	NO
Inventive step (IS)	Claims	2-3, 7-10, 21, 23	YES
	Claims	1, 4-6, 11-20, 22	NO
Industrial applicability (IA)	Claims	1-23	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 1, 4-6, 11-13, 17-20, and 22 lack novelty under PCT Article 33(2) as being anticipated by US 6,214,862 B1 (Fenteany et. al.), herein after Fenteany.

Regarding claim 1, Fenteany teaches the compound of claim 1 (col 2, ln 43 to col 3, ln 23). Using Fenteany's notation, present claim 1 teaches a structure where X1 = O, Z1 = NH, Z2= CH2CH2CH2Cl, Z3=NH, X2 = O, and A1 = CH2CHOHCH(CH3)2. Fenetany teaches that X1 can be O, Z1 can be NH, Z2 can be CHR where R1 is a C1-C6 haloalkyl (Here R1 would be a C2 Chloroalkyl). Fenetany teaches that Z3 can be NH; X2 = O, and A1 can be (CH)2(CHOH)(CH)(CH3)2.

Regarding claim 4, Fenteany teaches a pharmaceutically acceptable carrier or diluent (col 3, ln 23).

Regarding claim 5, claim 4 teaches a structure equivalent to claim 1 except that Z3 is N-CH(CH3)PMP, rather than NH. Fenteany teaches that Z3 can be a NR group. Additionally, Fenteany teaches a pharmaceutically acceptable carrier or diluent (col 3, ln 23).

Regarding claim 6, it teaches a structure similar to claim 5 except that Z2 is CH2CH2CHOH. Fenteany teaches that Z2 can be a C2-6 hydroxyl (in this case, this would be a C3hydroxyl) and Fenteany teaches a pharmaceutically acceptable carrier or diluent (col 3, ln 23).

Regarding claim 11, Fenteany teaches that compositions of the form of compound 3 can inhibit proteasome function in cells (Fenteany col 8, ln 38-49).

Regarding claim 12, Fenteany teaches these compositions can function in mammals (col 59, ln 1-24).

Regarding claim 13, Fenteany teaches these compositions can treat inflammation (col 58, ln 15-18).

Regarding claim 17, Fenteany also teaches this structure. The analysis is similar to that done for claim 1. Here, the only difference from the claim 1 analysis is that Z2 is composed of R4 and R5, where R4 is a halo-lower alkyl group and R5 is either hydrogen or a lower alkyl group. Fenteany teaches that R4 can be a halo-lower alkyl group (col 2, ln 64). The present claim R3 and R2 group encompases hydrogen, which is the same as the teaching of Fenteany, and the R1 group can be the same group previously considered in claim 1.

Regarding claim 18, the claimed R1 group is a side group off of group A1, taught by Fenteany. Fenteany teaches that his A group can encompass these cyclo groups (col. 3 lines 2-23).

Regarding claim 19, the claimed R1 group is a side group off of group A1, taught by Fenteany. Fenteany teaches that his A group can encompass straight chain hydrocarbons of this length (col. 3 lines 2-23).

Regarding claim 20, the claimed R2 group is equivalent to a R group off of Fenteny's Z1 group. Fenteny teaches that Z1 can be NR where this R (equivalent to the claimed R2 group), can be a C1-6 alkyl, which encompasses the structures (methyl, ethyl, etc.) taught by present claim 20.

Regarding claim 22, R4 is equivalent to an R side group off of Fenteny's Z2 group. Fenteny teaches that Z2 can be CHR1 where R1 is a C1-6 haloalkyl, which encompases the chloro, bromo or iodo ethyl, propyl, isopropyl etc. groups taught by present claim 22.

Claims 14-16 lack an inventive step under PCT article 33(3) as being obvious over Fenteany in view of Goldberg, "Not just research tools - proteasome inhibitors offer therapeutic promise" (hereafter Goldberg).

Regarding claim 14, Fenteany discloses that compounds such as compound 3 are effective at treating medical disorders, but fails to disclose ischemic or reperfusion injury. Goldberg discloses these uses (Goldberg page 340, col 1, para 2).

----------See Supplement Box----------

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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Citations and Explanation

Regarding claim 15, it would have been obvious to one of skill in the art that ischemia is a result of vascular occlusion.

Regarding claim 16, Goldberg discloses treating strokes (Goldberg page 340, col 1, para 2).

Claims 2 and 3 meet the criteria set out in PCT Article 33(2)-(3) because the prior art does not teach or fairly suggest the methods of synthesis of claims 2 and 3.

Claims 7-10, 21, and 23 meet the criteria set out in PCT Article 33(2)-(3) because the prior art does not teach the claimed structures.

Claims 1-23 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.